

Original
article

Valaciclovir for the suppression of recurrent genital HSV infection: a placebo controlled study of once daily therapy

R Patel, N J Bodsworth, P Woolley, B Peters, G Vejlsgaard, S Saari, A Gibb, J Robinson, and the International Valaciclovir HSV Study Group*

Objective: To determine the efficacy and safety of once daily valaciclovir for the suppression of recurrent genital herpes simplex virus (HSV) infection in immunocompetent patients.

Methods: 382 otherwise healthy patients with a history of frequently recurring genital HSV infection (eight recurrences per year) were randomly allocated to receive either oral valaciclovir (500 mg once daily) or placebo (3:1 ratio) for 16 weeks or until the first genital HSV recurrence, whichever occurred first. Patients were clinically assessed at regular intervals and also if they experienced a recurrence. Safety was evaluated through adverse experience reporting and monitoring of haematology and biochemistry variables. On completion of the double blind phase, patients were eligible for follow up to a maximum of 48 weeks' treatment with open label valaciclovir (500 mg once daily) for further safety monitoring. The results from the double blind phase of the study are reported here.

Results: A significant difference was detected between valaciclovir and placebo in the time to first recurrence of genital HSV infection. The hazard ratio [95% confidence interval] for valaciclovir *v* placebo was 0.155 [0.112, 0.214], $p < 0.0001$. Valaciclovir prevented or delayed 85% of the recurrences that would have occurred with placebo. After 16 weeks (day 112) with treatment, 69% of patients receiving valaciclovir were recurrence free compared with only 9.5% of patients assigned to placebo. The safety profiles of valaciclovir and placebo were comparable, with adverse experiences being infrequent and generally mild.

Conclusion: This study has demonstrated that once daily valaciclovir (500 mg), is highly effective and well tolerated for the suppression of recurrent genital HSV infection. Once daily dosing with valaciclovir provides a more convenient dosing regimen than the more frequent aciclovir regimens.

(*Genitourin Med* 1997;73:105-109)

Keywords: valaciclovir; herpes simplex virus; suppression

Royal South Hants
Hospital,
Southampton, UK
R Patel

Taylor Square Private
Clinic, Sydney,
Australia
N J Bodsworth

Withington Hospital,
Manchester, UK
P Woolley

Royal Free Hospital,
London, UK
B Peters

Rigshospitalet,
Copenhagen, Denmark
G Vejlsgaard

Laakariasema Pulssi,
Turku, Finland
S Saari

Glaxo Wellcome
Research and
Development,
Beckenham, UK
A Gibb
J Robinson

*Members of the group are
listed at the end of the
article.

Correspondence to:
Dr R Patel, Department of
GU Medicine, Royal South
Hants Hospital, Brintons
Terrace, Southampton,
Hants SO14 0YG, UK.

Accepted for publication
17 December 1996

Introduction

Genital herpes is a common sexually transmitted disease, the incidence of which has been seriously underestimated. Epidemiological surveys have indicated a marked increase in the seroprevalence of herpes simplex virus type 2 (HSV-2) in most regions of the world over the past 20 years.¹⁻³ The incidence of clinically diagnosed genital herpes is also increasing, with over half a million new cases reported annually in the USA.⁴ Although most genital herpes is caused by HSV-2 infection, evidence for an increase in disease caused by HSV-1 is also accumulating.⁵ HSV is now the most common cause of genital ulceration in many countries.⁶ Recurrent genital herpes is a frequent and distressing chronic condition, which can have a profound psychological and social impact on an individual.

Over 15 years of clinical experience has established aciclovir as the standard therapy for management of genital herpes.^{7,8} It is widely used for the treatment of primary and recurrent episodes and for long term suppression of recurrent episodes. Suppressive therapy is particularly appropriate in patients with frequent or severe recurrences and in those for whom the psychological impact of the disease is significant.⁹ Long term suppressive therapy is effective in reducing the frequency and

duration of recurrences of genital HSV infection.¹⁰⁻¹⁵ Studies of suppressive aciclovir therapy have now extended to 10 years and demonstrate that this form of management is effective and without serious adverse reactions.^{16,17}

Although aciclovir confers significant clinical benefit in the management of genital herpes, its limited oral bioavailability (10-20%) and short plasma elimination half life necessitate frequent dosing for optimal therapeutic effect. The optimal dose of aciclovir for suppressive therapy is considered to be 200 mg four times daily, although the more convenient 400 mg twice daily regimen is widely used to improve patient compliance. Once daily aciclovir is effective in a minority of patients but is clearly less effective than more frequent dosing regimens.¹⁸ However, frequent dosing is inconvenient in otherwise healthy subjects and may result in poor patient compliance particularly over long periods.¹⁹ In addition, a disease which may carry a social stigma requires sensitive and discreet treatment preferably in the privacy of a patient's home. A once daily therapy would provide the optimal regimen for the long term management of this disease.

Valaciclovir (Valtrex, Zelitrex), the L-valine ester of aciclovir, is rapidly and almost completely converted to aciclovir and the essential

amino acid, L-valine, after oral administration.²⁰ The bioavailability of aciclovir after administration of oral valaciclovir is three to five times greater than that following oral aciclovir itself.²⁰⁻²¹ Several studies have confirmed that valaciclovir is as effective as aciclovir for the acute or episodic treatment of HSV infection with a more convenient, less frequent dosing regimen and has a safety profile similar to that of aciclovir and placebo.²²⁻²³ The estimated aciclovir exposure (24 hour AUC) from valaciclovir, 500 mg once daily (47.7 $\mu\text{M}/\text{h}$) is approximately 1.5-fold greater than that achieved with oral aciclovir, 400 mg twice daily (approx 31 $\mu\text{M}/\text{h}$). The present study was performed to assess the efficacy of valaciclovir in a convenient once daily regimen for the suppression of recurrent episodes of genital HSV infection and to generate safety data on longer term use of valaciclovir.

Patients and methods

STUDY DESIGN

This was a multicentre, randomised, double blind, placebo controlled study of once daily valaciclovir for the suppression of recurrent HSV infection. Double blind therapy was given for 16 weeks or until the first HSV recurrence, whichever was first. After double blind therapy, patients were eligible to continue therapy in an open label follow up phase of once daily valaciclovir for a total treatment period of 48 weeks. The results from the double blind phase of the study are reported here.

PATIENT POPULATION

Male and female patients of at least 18 years of age were eligible to enter the study if they had a history of frequently recurring genital herpes with eight or more HSV recurrences per year. This recurrence rate could be assessed over a minimum of three months—for example, two or more recurrences in three months, etc. Those who had been receiving suppressive therapy with aciclovir must have stopped taking the drug and then suffered a recurrence within three months of stopping therapy. The recurrence also had to be within the three months before enrolment into the study. Patients were not eligible if they had significant hepatic or renal impairment, were pregnant or nursing mothers, were known to be immunocompromised, were hypersensitive to aciclovir or valaciclovir, or were receiving systemic or topical antiviral or immunomodulatory treatments. Ethics committee approval was obtained at each study site before recruitment commenced and all patients gave full written consent.

STUDY PROCEDURES

Eligible patients were screened then randomised to one of two treatment arms—oral valaciclovir 500 mg once daily or placebo once daily in a 3:1 ratio. Study treatment started immediately.

Blood samples were taken at screening for baseline haematology and clinical chemistry and a baseline physical examination was per-

formed. Pregnancy tests were performed on all women of childbearing potential at screening and also every eight weeks throughout the study. The date of the initial genital HSV episode and number of recurrences in the previous 12 months were also recorded.

Patients commenced double blind therapy at screening. They were then required to attend the clinic at four weekly intervals until week 16. Those patients who experienced a recurrence of genital HSV infection were to attend for clinical assessment within 24 hours of the first signs of HSV lesions (day one of the recurrence). If the lesions had reached at least the papular/vesicular stage of development, the double blind therapy was discontinued permanently and the episode was treated with open label valaciclovir, 500 mg twice daily for five days. For the purposes of this study, prodromal symptoms alone were not sufficient to define a recurrence. Patients returned to the clinic on day five of the recurrence for assessment of lesion healing and resolution of pain or other discomfort.

After 16 weeks of double blind therapy or after day five of the first recurrence of genital HSV infection, whichever event occurred first, patients were given open label valaciclovir, 500 mg once daily, until week 48 of the study. Diaries were used throughout the study for patients to record prodromal symptoms, any recurrences of genital HSV infection, any concomitant medications, and any adverse experiences.

Safety was assessed by adverse experience reporting at each clinic visit and from haematology (haemoglobin, white blood cell, and platelet counts) and clinical chemistry (creatinine, alkaline phosphatase and AST or ALT) evaluations at screening, and weeks 4, 32, 48, and at the end of the double blind phase. Safety information generated during the open label phase will be the subject of a separate report.

EFFICACY ENDPOINTS

The primary efficacy endpoint, on which the statistical sample size estimation was based, was the time from randomisation to the first recurrence of genital HSV infection during the double blind randomised phase of the study. Assuming that the hazard functions were proportional, the sample size of 198 patients in the valaciclovir treatment arm and 66 patients in the placebo arm provided 80% power to detect hazard ratios of 1.84 or greater or 0.54 or smaller at the 0.05 level of significance. This provided more than 80% power to detect an arithmetic difference of 0.4 (0.5 to 0.1) in the proportion of patients who were recurrence free at three months, assuming that 50% of the valaciclovir group were recurrence free at three months.²⁴ The sample size allowed for a 10% premature withdrawal rate.

STATISTICAL ANALYSIS

The primary efficacy analysis was an intent to treat comparison of once daily valaciclovir with placebo for data collected during the double blind phase of the study. The time to

Table 1 Demographic characteristics and disease history of patients

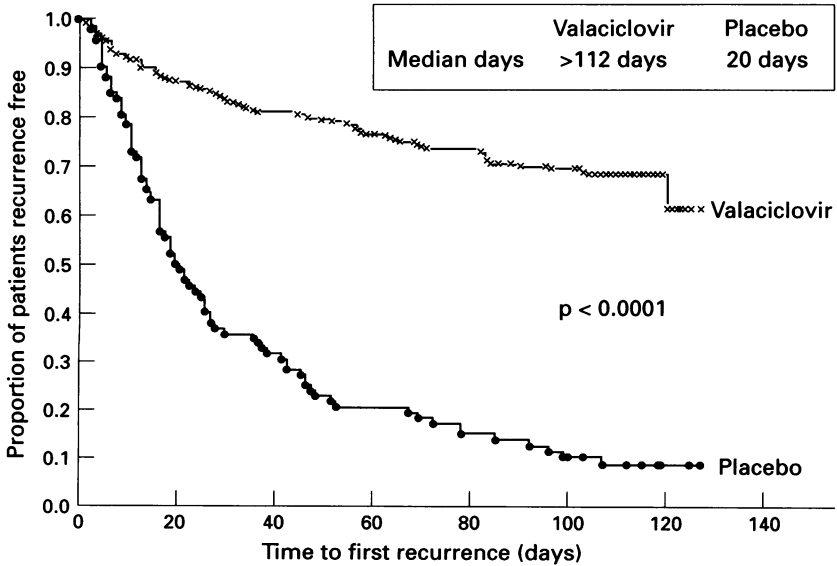
	Valaciclovir (n = 288)	Placebo (n = 94)
Median age (years) (range)	33 (19–79)	34 (19–80)
Sex (%) male/female	47/53	41/59
Median time from first episode HSV (years) (range)	5.1 (0.1–52.2)	3.8 (0.2–39.8)
HSV recurrence history when not receiving suppressive therapy—that is, recurrences per year (%):		
≤ 9	48	56
> 9	52	44
Use of suppressive aciclovir in previous year (%)	13	19
Median time on suppressive therapy (years) (range)	0.6 (0.2–7.1)	0.4 (0.2–1.6)

Table 2 Cox’s proportional hazards analysis of time to first HSV recurrence for the intent to treat group and HSV recurrence history subgroups

	Valaciclovir v placebo	
	Hazard ratio (95% CI)	p Value
Intent to treat	0.155 (0.112, 0.214)	< 0.0001
Subgroup		
≤ 9 recurrences/year	0.178 (0.107, 0.297)	—
> 9 recurrences/year	0.132 (0.083, 0.209)	—

first recurrence of HSV during the double blind phase was calculated relative to the day of randomisation. For patients who did not reach this endpoint, censored event free times were calculated to be equal to the last day that no event was recorded. Patients who completed the 16 weeks of the double blind phase without a recurrence had censored event free times equal to the end of the double blind phase.

The distribution of time to first recurrence was estimated using the Kaplan-Meier product limit method, and differences between treatment groups were estimated and tested using Cox’s proportional hazards model. Centre and previous HSV recurrence histories when not receiving suppressive therapy (≤ 9 or > 9 recurrences per year) were fitted as covariates in the proportional hazards model. Other covariates investigated included sex, age (< 34 or ≥ 34 years), and time since first HSV episode (< 5 or ≥ 5 years). All tests were two sided. The relation between HSV recurrence history and treatment effect was explored further by performing a subgroup analysis.



Kaplan-Meier plots of time to first HSV recurrence.

Differences between treatments or changes over time in haematology or clinical chemistry were assessed from quartile plots of each variable from samples obtained at clinical visits. The 95% confidence intervals and Hodges-Lehmann estimates were used to determine any treatment differences at each scheduled visit.

Results

PATIENT CHARACTERISTICS

In total, 382 patients were randomised to treatment at 34 study sites in Europe and Australasia. Of these, 288 received valaciclovir and 94 received placebo. The demographic characteristics and HSV disease history at screen are shown in table 1 and were similar in the valaciclovir and placebo groups. The sex split was comparable in both groups; ages ranged from 19 to 80 years (median 34 years). HSV disease history was similar in the two groups with 52% of patients having > 9 recurrences per year when not receiving suppressive therapy. The median time from the initial HSV episode was approximately 4.9 years. Overall, 14% had received suppressive aciclovir therapy in the previous year for a median time of six months. A positive diagnosis of genital HSV based on culture, direct antigen testing, or immunofluorescence assay was available for 90% of patients before enrolment.

ANALYSIS OF EFFICACY

A total of 382 patients were included in the intent to treat analysis. The intent to treat analysis of time to first genital HSV recurrence detected a significant difference between valaciclovir and placebo, as indicated by the hazard ratio (95% confidence interval) of 0.155 (0.112, 0.214), $p < 0.0001$ (table 2). Thus, valaciclovir treatment prevented or delayed 85% of the recurrences that occurred in patients receiving placebo during the double blind study period. At the end of 16 weeks (day 112) the Kaplan-Meier proportions of patients recurrence free were 69% for patients receiving valaciclovir and 9.5% for those receiving placebo. The median time to first HSV recurrence for patients receiving placebo was 20 days. For the valaciclovir group, the median was estimated to be > 112 days since the majority of patients were still recurrence-free at day 112 (figure). An analysis of treatment differences in the two subgroups (≤ 9 and > 9 recurrences per year) indicated a consistent benefit of valaciclovir irrespective of HSV recurrence history (table 2). For patients with ≤ 9 recurrences per year, valaciclovir prevented or delayed 82% of the recurrences experienced by patients receiving placebo [hazard ratio 0.178 (0.107, 0.297)]. In the subgroup of patients with > 9 recurrences per year, valaciclovir prevented or delayed 87% of the recurrences experienced by placebo recipients [hazard ratio 0.132 (0.083, 0.209)].

Further exploratory analyses showed that, of all the prognostic factors, only time from primary episode and HSV recurrence history

Table 3 Cox's proportional hazards analysis of time to first HSV recurrence for prognostic factors influencing time to first recurrence

Factor	Hazard ratio (95% CI)	p Value
Valaciclovir v placebo	0.149 (0.108, 0.206)	< 0.0001
HSV recurrence history (≤ 9 v > 9 recurrences/year)	0.716 (0.514, 0.996)	0.0473
Time since primary episode (< 5 v ≥ 5 years)	0.718 (0.514, 1.003)	0.0519

Table 4 Adverse experiences, without regard to causality, reported by $\geq 5\%$ of patients in either treatment group

Adverse experience	% Patients reporting*	
	Valaciclovir (n = 288)	Placebo (n = 94)
Headache	23	13
Nausea	9	9
Rhinitis	7	11
Infection	7	4
Flu-like syndrome	6	4
Diarrhoea	5	4
Back pain	5	1
Rash	5	5
Pharyngitis	5	3
Vaginal candidiasis	5	1
Abdominal pain	5	2
Pain	1	5

Reported % are not adjusted to take account of the difference between treatment groups in the total period of safety monitoring.

appeared to influence the HSV recurrence rate (table 3). The results suggest that those patients whose primary episode was within five years experienced a reduced recurrence rate (28% lower) than those whose primary episode was (five years ago [hazard ratio 0.718 (0.514, 1.003)]. Not surprisingly, the recurrence rate for patients with a history of ≤ 9 recurrences per year was 28% lower than that for those with > 9 recurrences per year [hazard ratio 0.716 (0.514, 0.996)].

Since patients ceased double blind therapy once they experienced a genital herpes recurrence, the total period of safety monitoring was shorter in the placebo group (3264 patient days) than in the valaciclovir group (24 496 patient days). The overall adverse experience reporting rate was similar between the two groups: 0.02 per patient day for valaciclovir and 0.03 per patient day for placebo. The adverse experience profile of valaciclovir was similar to that of placebo (table 4). Most adverse experiences were of mild intensity. Only headache and nausea were reported by $\geq 9\%$ of the patients in both treatment groups. There was only one serious adverse experience reported during the double blind phase (intestinal obstruction in a valaciclovir recipient) and this was not considered attributable to study medication. There were no clinically significant differences between treatment groups with regard to the distribution or changes from screen for any clinical chemistry or haematology variable.

Discussion

The worldwide incidence of genital herpes is increasing rapidly despite the raised public awareness of sexually transmitted diseases through health education programmes.¹² Antiviral therapy for the management of recurrent genital HSV infections may be episodic, whereby each outbreak is treated as it occurs, or for patients with more frequent or severe recurrences or those in whom the psychological impact is significant, suppressive therapy

may be advocated. Prevention of outbreaks may significantly improve a patient's quality of life. For prophylaxis or prevention of disease symptoms in otherwise healthy subjects, once daily dosage regimens have proved optimal and ensure better compliance.¹⁹ Dosing convenience is of particular importance for a potentially socially stigmatising sexually transmitted disease like genital herpes where patients often prefer to take medication in the privacy of their own home.

This study is the first evaluation of valaciclovir for the suppression of genital HSV infection. It has demonstrated that once daily valaciclovir is highly effective at preventing or delaying recurrences of genital herpes and is well tolerated, having a similar safety profile to that of placebo.

The patients included in this trial had previously suffered at least eight recurrences of genital herpes per year. A double blind study period of four months meant that without active treatment, nearly all patients would suffer a recurrence, therefore allowing a convincing demonstration of the efficacy of once daily valaciclovir.

Valaciclovir prevented or delayed on average 85% of the recurrences experienced by patients receiving placebo [hazard ratio (95% confidence interval) 0.155 (0.112, 0.214)]. At the end of the 16 weeks, 69% of valaciclovir recipients but only 9.5% of placebo recipients were recurrence free. This is comparable with the results of previous studies of aciclovir (400 mg twice daily) in similar patient populations where 68–80% of patients were recurrence free at three months.^{12–14} The benefit of once daily valaciclovir was similar in the subgroups of patients having histories of ≤ 9 and > 9 recurrences per year where recurrence frequency was reduced by 82% and 87% respectively. This study demonstrates that valaciclovir can maintain efficacy with a once daily dosage probably as a result of the enhanced aciclovir bioavailability from valaciclovir. Prospective, controlled trials to establish the efficacy of different doses of valaciclovir are ongoing.

The investigation of a number of predefined key prognostic factors on the primary efficacy endpoint ensured adjustment for any imbalances between treatment groups as well as investigating the effect of these factors on treatment outcome. Of those factors investigated, only time since first episode of genital herpes and (as expected) frequency of recurrences in the previous year influenced time to first recurrence in this study. Exploratory analysis suggests that patients whose primary episode was within five years of randomisation into the study experienced a 28% lower recurrence rate compared with those whose primary episode was ≥ 5 years ago. One explanation may be that patients who are still attending a clinic for their HSV disease ≥ 5 years after their primary episode may be those who have more severe herpes infection.

In otherwise healthy adults, safety is a particularly important consideration, especially when therapy may be extended or used repeatedly over long periods of time. The safety profile of valaciclovir was highly acceptable with

adverse experiences being infrequent and usually mild. Additional safety information on chronic dosing is being generated in the open label follow up phase of this study. Adverse event reports were typical of those in previous studies of aciclovir and valaciclovir versus placebo, with headache and nausea being the most common. Taking into account the different exposures to valaciclovir and placebo, the overall adverse experience rates were similar at 0.02 per patient day in the valaciclovir group and 0.03 per patient day in the placebo group. In previous placebo controlled trials of oral aciclovir or valaciclovir in the acute treatment of recurrent HSV infections and zoster, adverse experiences occurred in similar proportions of patients receiving the active treatments and placebo, suggesting that such events are often typical features of the disease rather than the result of treatment.²²⁻²⁵⁻²⁹ Laboratory safety monitoring also indicated that valaciclovir was well tolerated with no clinically significant effects on haematological or biochemical factors.

This present study demonstrates that once daily valaciclovir is effective in delaying the time to first HSV recurrence and reducing the rate of HSV recurrences. Such a marked suppressive effect has not previously been demonstrated with once daily antiviral therapy. Thus, valaciclovir provides marked clinical efficacy and highly acceptable safety as suppressive therapy for recurrent HSV infection, with the advantage of a once daily regimen.

The authors and the International Valaciclovir HSV Study Group gratefully acknowledge Glaxo Wellcome for financial support and assistance with the conduct of this study. We are particularly indebted to H Watt and A Gibb for the statistical design and analysis, and S C Oakes, A R Bell, and R J Crooks for their contribution to the design and conduct of the study and preparation of this manuscript.

The International Valaciclovir HSV Study Group

S Barton, Chelsea and Westminster Hospital, London, UK; N Bodsworth, Taylor Square Private Clinic, Sydney, Australia; J Chuah, Gold Coast Sexual Health Centre, Miami, Australia; E Curless, Bolton General Hospital, Bolton, UK; J Delescluse, Clinique Cesar de Paepe, Brussels, Belgium; C Duncombe, Holdsworth House General Practice, Sydney, Australia; J Esmann, Marselisborg Hospital, Århus, Denmark; L Fahraeus, Universitetssjukhuset, Linköping, Sweden; G Fierlbeck, Universitäts Hautklinik, Tübingen, Germany; M Geniaux, Hôpital Pellegrin-Tripode, Bordeaux, France; G Gross, Universitäts-Hautklinik und Poliklinik, Hamburg, Germany; P Horner, Bristol Royal Infirmary, Bristol, UK; S Kroon, Odense Sygehus, Odense, Denmark; C Law, St George Hospital, Kogarah, Australia; G McKenna, Christchurch Hospital, Christchurch, New Zealand; B Milpied-Homsi, CHR de Nantes, Nantes, France; H Moi, Olafiaklinikken, Oslo, Norway; P Morel, Hôpital St Louis, Paris, France; E Morgan, St Lukes Hospital, Bradford, UK; F Mulcahy, St James Hospital, Dublin, Ireland; R Patel, Royal South Hants Hospital, Southampton, UK; J Paavonen, Helsinki University Hospital, Helsinki, Finland; B Peters, Royal Free Hospital, London, UK; J Roed-Petersen, KAS Gentofte, Gentofte, Denmark; K Ryberg, Uddevalla Sjukus, Uddevalla, Sweden; S Saari, Laakariasema Pulssi, Turku, Finland; A-L Simpanen, Laboratoria Simpanen, Kuopio, Finland; A Strand, Akademiska Sjukhuset, Uppsala, Sweden; D Timmins, Royal Liverpool Hospital, Liverpool, UK; G Vejlsgaard, Rigshospitalet, Copenhagen, Denmark; N von Uexkull, Lakarhuset Hotorget, Stockholm, Sweden; E Weissenbacher, Klinikum Grosshadern, Munich, Germany; P Woolley, Withington Hospital,

Manchester, UK; A-M Worm, Bispebjerg Hospital, Copenhagen, Denmark.

- 1 Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and sociological patterns of herpes virus infection in the world. *Scand J Infect Dis Suppl* 1990; 69:19-36.
- 2 Johnson RE, Nahmias AJ, Magder LS, Lee FK, Brooks CA, Snowden CB. A seroepidemiological survey of the prevalence of herpes simplex virus type-2 infection in the United States. *N Engl J Med* 1989;321:7-12.
- 3 Corey L. The current trend in genital herpes. *Sex Transm Dis* 1994; **Suppl** 2: S38-44.
- 4 Mertz GJ. Herpes simplex virus. In: Galasso GJ, Whitley RJ, Merigan TC, eds. *Antiviral agents and viral diseases of man*. 3rd ed. New York: Raven Press, 1990.
- 5 Kinghorn GR. Genital herpes: natural history and treatment of acute episodes. *J Med Virol* 1993; **Suppl** 1:33-8.
- 6 Corey L. Genital herpes. In: Holmes KK, Mardh PA, Sparling PF, Weisner PJ, eds. *Sexually transmitted diseases. Part 5 Sexually transmitted agents*. New York: McGraw-Hill, 1990.
- 7 Wagstaff AJ, Faulds D, Goa KL. Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994;47:153-205.
- 8 Whitley RJ, Gnaan JW. Acyclovir: a decade later. *N Engl J Med* 1992;327:782-9.
- 9 Carney O, Ross E, Ikkos G, Mindel A. The effect of suppressive oral acyclovir on the psychological morbidity associated with recurrent genital herpes. *Gonorrhea Med* 1993;69:457-9.
- 10 Kinghorn GR. Long-term suppression with oral acyclovir of recurrent herpes simplex virus infections in otherwise healthy patients. *Am J Med* 1988;85 (Suppl 2A):26-9.
- 11 Straus SE, Croen KD, Sawyer MH, Freifeld AG, Felsner JM, Dale JK, et al. Acyclovir suppression of frequently recurring genital herpes. *JAMA* 1988;260:2227-30.
- 12 Kroon S, Petersen CS, Andersen LP, Ronne Rasmussen J, Vestergaard BF. Oral acyclovir suppressive therapy in severe recurrent genital herpes. *Dan Med Bull* 1989; 36:298-300.
- 13 Mertz GJ, Jones CC, Mills J, Fife KH, Lemon SM, Stapleton JT, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection. *JAMA* 1988;260:201-6.
- 14 Mattison HR, Reichman RC, Benedetti J, Bolgiano D, Davis LG, Bailey-Farchione A, et al. Double-blind placebo-controlled trial comparing long-term suppressive with short-term oral acyclovir therapy for management of recurrent genital herpes. *Am J Med* 1988;85 (suppl 2A):20-5.
- 15 Douglas JM, Critchlow C, Benedetti J, Mertz GJ, Connor JD, Hintz MA, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. *N Engl J Med* 1984;310:1551-6.
- 16 Tilson HH, Engle CR, Andrews EB. Safety of aciclovir: a summary of the first 10 years' experience. *J Med Virol* 1993;1:67-73.
- 17 Baker DA, Safran S, Deeter RG, Walker A, Barton G, and the Acyclovir Study Group. Nine year effectiveness of continuous suppressive therapy with acyclovir (ACV) in patients with recurrent genital herpes (RGH). *J Eur Acad Dermatol Venereol* 1995;5 (Suppl 1): S169.
- 18 Mindel A, Carney O, Freris M, Faherty A, Patou G, Williams P. Dosage and safety of long-term suppressive acyclovir therapy for recurrent genital herpes. *Lancet* 1988;i:926-8.
- 19 Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przyback TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990;150:1881-4.
- 20 Weller S, Blum MR, Doucette M, Burnette T, Cederberg DM, de Miranda P, et al. Pharmacokinetics of the aciclovir prodrug valaciclovir after single- and multiple-dose administration in normal volunteers. *Clin Pharmacol Exp Ther* 1993;54:595-605.
- 21 Soul-Lawton S, Seaber E, On N, Wootton R, Rolan P, Posner J, et al. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of aciclovir, following oral administration to humans. *Antimicrob Agents Chemother* 1995;39:2759-64.
- 22 Spruance SL, Tyring SK, Degregorio B, Miller C, Beutner K, and the Valaciclovir Study Group. A large scale placebo-controlled trial of peroral valaciclovir for episodic treatment of recurrent herpes genitalis. *Arch Intern Med* 1996;156:1729-35.
- 23 Kinghorn GI, Fiddian AP, and the Valaciclovir International HSV Study Group. Prevention of lesion development in recurrent genital herpes with oral valaciclovir. *J Eur Acad Dermatol Venereol* 1995;5:S162.
- 24 Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med* 1982;1: 121-9.
- 25 Goldberg LH. Oral acyclovir for episodic treatment of recurrent genital herpes: efficacy and safety. *J Am Acad Dermatol* 1986;15:256-64.
- 26 Huff JC, Bean B, Balfour HH Jr, Laskin OL, Connor JD, Corey L, et al. Therapy for herpes zoster with oral acyclovir. *Am J Med* 1988;85:84-9.
- 27 Morton P, Thomson AN. Oral acyclovir in the treatment of herpes zoster in general practice. *NZ Med J* 1989;102: 93-5.
- 28 Wood MJ, Ogan PH, McKendrick MW, Care CD, McGill JJ, Webb EM. Efficacy of oral acyclovir treatment of acute herpes zoster. *Am J Med* 1988;85:79-83.
- 29 Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL, Wood MJ. Valaciclovir compared with acyclovir for improved therapy of herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother* 1995;39:1546-53.